Squamous and Sebaceous Lesions of Conjunctiva: Advances in Immunohistochemical and Molecular Markers

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AAOP/USCAP 2010
Washington DC
Overview

• Conjunctival Intraepithelial Neoplasia (CIN) and Squamous Cell Carcinoma
• Conjunctival Spindle Cell Carcinoma
• Sebaceous Carcinoma
Conjunctival Intraepithelial Neoplasia (CIN)

- Older individuals, M>F
- Associated with sun exposure, HIV, HPV
- Generally involve perilimbal conjunctiva
- Sharply demarcated
- Can recur and progress to SCC
Conjunctival Squamous Cell Carcinoma
Conjunctival Intraepithelial Neoplasia (CIN)

• Proposed prognostic markers: p53, Ki67, AgNOR

• Other roles of special stains:
  – Rule out melanocytic lesions (Melan A, MITF, etc.)
  – Rule out sebaceous carcinoma on frozen material (Oil Red O)
  – Look for HPV (in situ)
HPV in Conjunctival CIN and Squamous Cell Carcinoma

- Several studies suggested that “high risk” HPV is often present
- Other studies failed to detect HPV
- It has recently been suggested that the “cutaneous” HPV types 5 and 8 are involved
Human Papillomavirus 16 and 18 Expression in Conjunctival Intraepithelial Neoplasia

Ingrid U. Scott, MD, MPH,1 Carol L. Karp, MD,1 Gerard J. Nuovo, MD2
Ophthalmology Volume 109, Number 3, March 2002

Human papilloma virus in neoplastic and non-neoplastic conditions of the external eye

Zeynel A Karciglu, Tawfik M Issa

HPV 16 or HPV 18 DNA and mRNA detected in 10/10 CIN and no controls

HPV 16 or HPV 18 DNA detected in 25 of 45 (56%) in situ and invasive conjunctival SCC, but also in 32% of normal conjunctival specimens.
HPV in Conjunctival CIN and Squamous Cell Carcinoma

• Several studies suggested that “high risk” HPV is often present
• Other studies failed to detect HPV
• It has recently been suggested that the “cutaneous” HPV types 5 and 8 are involved
No HPV DNA detected in 30 cases of CIN and SCC

No Evidence for a Pathogenic Role of Human Papillomavirus Infection in Ocular Surface Squamous Neoplasia in Germany

24 consecutive cases of CIN and SCC from a single institution examined using IHC and PCR. 15 HPV subtypes analyzed – none detected.
HPV in Conjunctival CIN and Squamous Cell Carcinoma

• Several studies suggested that “high risk” HPV is often present
• Other studies failed to detect HPV
• It has recently been suggested that the “cutaneous” HPV types 5 and 8 are involved
• Study in Uganda involving 94 conjunctival SCC, 39 CIN, and 285 controls
• PCR tests for 75 HPV types used
• “Mucosal” HPV rare or absent
• “Cutaneous” HPV (especially types 5 and 8) identified in 45% of SCC and 41% of CIN
• Cutaneous HPV infection and squamous conjunctival lesions seldom seen in the absence of HIV
Conjunctival Spindle Cell Carcinoma
Sebaceous Carcinoma

- Rare (1% to 3% of all malignant eyelid tumors)
- Elderly individuals (F>M)
- Often multicentric
- Prominent intraepithelial spread

Shields and Shields
Intraepithelial Sebaceous Carcinoma
EMA and p16 Immunostains in Sebaceous Carcinoma
p16 Highlights Intraepithelial Spread
Adipophilin expression in sebaceous tumors and other cutaneous lesions with clear cell histology: an immunohistochemical study of 117 cases

Daniel A Ostler¹, Victor G Prieto²,³, Jon A Reed¹, Michael T Deavers², Alexander J Lazar²,³ and Doina Ivan²,³
Adipophilin can distinguish sebaceous tumors from basal cell carcinoma and squamous lesions.
Mismatch Repair in Sebaceous Carcinoma

• Sebaceous gland tumors and visceral malignancies (most frequently colorectal carcinoma) occur together in Muir-Torre syndrome (MTS)
• Sebaceous adenoma more common than carcinoma
• Mutations in MLH1, MSH2 and other genes associated with DNA mismatch repair
61 year old female with MTS
Our experience with MMR gene IHC and MSI in sporadic sebaceous carcinoma

• 9 sporadic cases stained with antibodies specific for MSH2, MSH6, MLH1 and PMS2
• No loss of staining in any sporadic tumor
• Also no signs of microsatellite instability (MSI) in any sporadic sebaceous carcinoma case tested by PCR analysis of multiple markers
Site and Tumor Type Predicts DNA Mismatch Repair Status in Cutaneous Sebaceous Neoplasia

Rajenda S. Singh, MD,* Wayne Grayson, MBChB/PhD, FCPath(SA),† Mark Redston, MD,‡ A. Hafeez Diwan, MD, PhD,* Carla L. Warneke, MS,§ Phillip H. McKee, MD, FRCPath,‖ Dina Lev, MD,¶ Stephen Lyle, MD, PhD,‖ Eduardo Calonje, MD, Dip RCPath,# and Alexander J. F. Lazar, MD, PhD*

FIGURE 2. Anatomic distribution of sebaceous adenomas (A), sebaceous carcinomas (B), or all sebaceous neoplasms outside the head and neck area (C), indicating whether tumors are MMR-intact (MMRI, open circle) or MMR-deficient (MMRD, closed, black circle). A and B. The nonhead and neck lesions are grouped in the lower right aspect.
Different Genetic Pathways in the Development of Periocular Sebaceous Gland Carcinomas in Presumptive Muir-Torre Syndrome Patients

M. Goldberg, C. Rummelt, S. Foja, L.M. Holbach, and W.G. Ballhausen

FHIT may be involved in Muir-Torre cases lacking MSH/MLH changes

FIGURE 4. Proposed model of genetic pathways involved in the development of periocular SGCs in presumed MTS patients.
Epidermal growth factor receptor (EGFR) expression in periocular and extraocular sebaceous carcinoma

Table 1. EGFR expression in periocular and extraocular sebaceous carcinoma

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<tr>
<th>Score</th>
<th>Periocular</th>
<th>Extraocular</th>
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<tbody>
<tr>
<td>0 (≤5%)</td>
<td>9 (47.4%)</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>1 (5–25%)</td>
<td>7 (36.8%)</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>2 (26–75%)</td>
<td>2 (10.6%)</td>
<td>3 (17.6%)</td>
</tr>
<tr>
<td>3 (&gt;75%)</td>
<td>1 (5.2%)</td>
<td>12 (70.6%)</td>
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Score 0: ≤5% positive cells; score 1: 5–25% positive cells, score 2: 26–75% positive cells and score 3: >75% positive cells.

Fig. 2. EGFR expression (>75% cells, 3+ intensity) in one of the extraocular sebaceous carcinomas.
Conclusions

• The role of HPV in the pathogenesis of CIN and conjunctival squamous cell carcinoma is not clear
• p16 immunostains can be useful in tracking intraepithelial spread of sebaceous carcinoma
• Immunohistochemical stains suggest an intact mismatch repair system in sporadic periocular sebaceous carcinoma